PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SBRI124055	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2004/043023	International filing date *(day/month/year)* 20.12.2004	Priority date *(day/month/year)* 19.12.2003
International Patent Classification (IPC) or national classification and IPC C07K14/445, C12N15/30, A61K39/015		
Applicant SEATTLE BIOMEDICAL RESEARCH INSTITUTE et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.09.2005	22.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Voigt-Ritzer, H Telephone No. +49 89 2399- 7187

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/043023

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-25 as originally filed

   Sequence listings part of the description, Pages

   1-3 as originally filed

   Claims, Numbers

   1-5 as originally filed

   Drawings, Sheets

   1/1 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/043023

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 2,4

because:

☒ the said international application, or the said claims Nos. 2,4 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-5
	No:	Claims	1
Inventive step (IS)	Yes:	Claims	
	No:	Claims	2-5
Industrial applicability (IA)	Yes:	Claims	1,3,5
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Reference is made to the following documents:

D1: SULTAN ALI A ET AL: "TRAP is necessary for gliding motility and infectivity of Plasmodium sporozoites" CELL, vol. 90, no. 3, 1997, pages 511-522

D2: MENARD ROBERT ET AL: "Circumsporozoite protein is required for development of malaria sporozoites in mosquitoes" NATURE (LONDON), vol. 385, no. 6614, 1997, pages 336-340

D3: MATUSCHEWSKI KAI ET AL: "Infectivity-associated changes in the transcriptional repertoire of the malaria parasite sporozoite stage." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 44, 1 November 2002 (2002-11-01), pages 41948-41953

D4: MENARD R ET AL: "Gene Targeting in Malaria Parasites" METHODS : A COMPANION TO METHODS IN ENZYMOLOGY, ACADEMIC PRESS INC., NEW YORK, NY, US, vol. 13, no. 2, October 1997 (1997-10), pages 148-157

D5: VAN DIJK MELISSA R ET AL: "A central role for P48/45 in malaria parasite male gamete fertility" CELL, vol. 104, no. 1, 12 January 2001 (2001-01-12), pages 153-164

The present application pertains a malaria vaccine based on live Plasmodium parasites that have been genetically attenuated by deletion of a liver-stage specific gene function. *uis3* and *uis4* knockout Plasmodium parasites have been constructed and successfully used to protect mice from wt Plasmodium infection.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 2 and 4 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT). For the assessment of these claims on the question whether they are industrially

applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty

A difference between claim language and intended meaning (according to the description page 3) can be detected for "a liver-stage specific gene function".
According to the description "a liver-stage specific gene function" is one that is:
-required to transform sporozoites into merozoites and erythrocytic stages
-not required for entry into hepatocytes or maintenance of parasite in asexual erythrocyte stage and production of infective sporozoites
These parameters of a liver-stage specific gene function however are not mentioned in the claims. There is hence a problem concerning clarity of claims 1-6.
In the light of the broad claim language the following novelty objections are raised.

- Document D1 discloses *trap* knockout Plasmodium parasites and is novelty destroying for the subject-matter of claim 1.
TRAP is critical for sporozoite infection of the mosquito salivary gland and the rat liver, and is essential for sporozoite gliding motility in vitro. *trap* knockout sporozoites are completely deficient in hepatocyte invasion. Yet they can still initiate blood stage infection when inoculated at high doses.
- Document D2 reveals the disruption of the CS gene. The CS is essential for sporozoite formation within oocytes in the mosquito and in the vertebrate host it promotes sporozoite attachment to hepatocytes (D2, abstract). Consequently does the *cs* knockout Plasmodium parasite disclosed in D2 destroy novelty for the subject-matter of claim 1.

Consequently is the subject-matter of claim 1 not new.

Inventive step

Liver stage antigens have been shown to be important by demonstrating that immunisation with irradiated (attenuated) sporozoites could induce protective immunity. However, there may be hundreds or thousands of antigens that contribute to the sterile protective immunity elicited by irradiated sporozoite vaccine.

Some liver stage antigens have been identified so far.

It has been postulated that CS, SAP-2 and LSA-1 as well as LSA-3 proteins are involved in the pathogen's initial interaction with hepatocyte surface. Another protein, SALSA is transcribed during the sporozoite stage with an increases throughout the whole hepatic schizogony stage.

Developmental upregulation of specific mRNAs in certain life-cycle stages indicates that their translation products may have unique roles in hepatocyte infection and/or development of liver stages. In this context the authors of document D3 found that UIS genes are stage-specifically upregulated. They suggest that these genes can be targeted by reverse genetics since the corresponding proteins might perform crucial functions. The authors further suggest a functional complementation of *uis* knockout parasites (D3).

The recent advent in gene targeting technology in Plasmodium allows the skilled person to use a genetic approach for analysis of gene function and vaccine development. In this respect document D4 discloses vector design, types of mutations that can be generated in a target locus as well as screening strategies.

Targeted blood stages of the parasite as well as sporozoites have been characterized in the past for their phenotypes in order to conclude for their role.

The disruption of CS gene in P. berghei has shown that CS is essential for sporozoite formation within oocytes as well as for hepatocyte invasion (D2).

Gene disruption of the gamete protein PFS48/45 demonstrates that the protein plays an important role in fertilization. Male gametes pf p48/45- parasites failed to penetrate otherwise fertile female gametes (D5).

And finally the disruption of the liver stage protein TRAP abolishes sporozoite gliding motility, the sporozoites are furthermore completely deficient in hepatocyte invasion (D1).

The person skilled in the art would be motivated to target or arrest the hepatic stage of Plasmodium life cycle because this would prevent the clinical symptoms of malaria (erythrocyte stage) as well as the transmission of malaria (sexual stage). In other words, the most effective malaria vaccine that would result in sterilizing protective immunity would be directed towards eliminating or arresting the parasite inside the liver cells.

Therefore, by combining the teaching of D3 with the knowledge of a successful whole cell vaccine with wt sporozoites the person skilled in the art would be motivated to continue in this direction and arrive at the claimed invention.
Consequently does the subject-matter of claims 2-5 not fulfil the requirements of inventive step.